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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,665	12/16/2002	Philip O. Livingston	2653/56	9377

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,665	LIVINGSTON ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 35-39 are being examined.

Objection

Claim 48 remains objected for the use of the language "CpG".

Applicant argues that "CpG" is not an abbreviation, and thus is not amended.

The Examiner apologizes that "CpG" was inadvertently recited as an abbreviation. Objection however remains, because it not clear what CpG is. This objection could be obviated by amending the claim 48, for example, to recite for example, "CpG, which is an immunostimulatory motif".

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

Claims 39-59 remain rejected under 112, first paragraph for lack of enablement for a method for treating small cell lung cancer or neuroblastoma, comprising administering polymers of alpha-(2-8)-polysialic acid conjugated to a carrier, and an adjuvant, for reasons already of record in paper of 11/02/05.

Applicant argues that the cited references are directed to general area of cancer treatment, and not the particular types of treatment being claimed. Applicant argues that for example, Gura and Hartwell are concerned with screening for new drugs, which is not required in the claimed

invention. Applicant argues that Jain does not discuss the use of compositions to stimulate an immune response against tumor cells. Applicant argues that Curti is concerned with chemotherapeutic drugs, which act in a very different manner from the alpha-(2-8)-polysialic acid-carrier conjugate used in the claimed method. Applicant argues that Ezzel and Spitler do not deal with the particular methods being claims, and that general doubts on vaccines says nothing about the enablement of the claimed methods. Applicant argues that Boon focus on the problem of tolerance, which is overcome by the present invention.

Applicant's arguments in paper of 05/05/06 have been considered but are not found to be persuasive for the following reasons:

The claimed method encompasses an immunotherapy method for treating cancer, in which the production of antibodies against the cancer cells in a cancer patient is elicited by the administration of a cancer cell antigen, alpha-(2-8)-polysialic acid. Although the cited references do not specifically recite the problem of treating small cell lung cancer or neuroblastoma, using alpha-(2-8)-polysialic acid-carrier conjugate, however, the cited references apply as well to the claimed invention, because they discuss the refractory problem with cancer treatment in general, such as the references by Gura, Jain, Curti, and Hartwell, or the unpredictability of immunotherapy in particular, such as the references by Ezzell, Spitler, Boon, and White et al. For example, Ezzell clearly teaches that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6). Spitler teaches that cancer vaccines, which is supposed to induce tumor immunity to prevent tumor recurrence, and to eliminate residual diease, usually

do not work. Boon teaches that several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). In addition, Boon teaches even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph). In the instant application, although the specification discloses that antibodies against the cancer antigen, alpha-(2-8)-polysialic acid are produced, there is no evidence that the antibodies are produced in sufficient quantities to effectively reduce cancer cell growth of the treated patients. In other words, the issue taught by Boon, i.e. whether the cancer burdens at least depress the capability to respond against the tumor is clearly applicable to the instant invention. Similarly, there is no evidence that the antibodies produced are effective against the primary cancer cells in treated patients. Thus the issue of unpredictability due to inconsistencies in antigen expression or presentation by tumor cells taught by Boon, and the issue of whether the antigens shed, modulate or internalize, all of which influence the effectiveness of the antibody, taught by White, clearly apply to the instant invention.

Applicant argues that as cited in the specification on page 2, lines 8-11, Zhang, 1997, teach that polysialic acid is distributed on small cell lung cancer (SCLC) and neuroblastoma cells. Applicant argues that the problem with cell culture artifacts will not effect the enablement of the present invention. Applicant argues that Examples 2-3 provide data, in part from human clinical trials, which show that antibodies raised by the claimed methods can recognize and even lyse tumor cells having the relevant polysialic acid antigens.

The recitation of Zhang is acknowledged.

The arguments are not found to be persuasive. One cannot extrapolate from ***in vitro*** lysis of a cancer cell line to a successful treating of patients having small cell lung cancer or neuroblastoma. In Example 2, on page 16-17, administration of polysialic acid and an adjuvant in mice produces antibodies, that recognize polysialic acid on a cancer cell line and cause complement-mediated lysis of said cancer cell in vitro. In Example 3, on pages 17-19, although the antibodies are produced in treated patients with small cell lung cancer, the example only shows that the antibodies bind a small cell lung cancer cell line. There is however no indication that said antibodies are produced in sufficient quantity and effective in reducing growth of small cell lung cancer in these patients, as response such as reducing cancer cell growth in the presence of the antibodies in these patients is not reported in the specification. Further, although Zhang teach that small cell lung cancer and neuroblastoma express polysialic acid, one cannot predict that the polysialic acid antigen is a suitable in vivo target, because of the problem of whether the antigens shed, modulate or internalize, which problem would influence the effectiveness of the administered antibody, as taught by White et al, of record, cannot be predicted. In addition, although the antibodies could lyse a cancer cell line, however, in view that characteristics and response of primary cancer cells and those in culture are different, and further in view that in vivo conditions are complex and cannot be extrapolated from in vitro conditions, as taught by Drexler et al, Embleton et al, Hsu, Tian et al, Van Dyke et al, all of record, one cannot predict that the antibodies are produced in sufficient quantity and would be effective in killing primary small cell lung cancer or neuroblastoma in vivo. This unpredictability is further evidenced by Kimmel et al, 1987 (J. Neurosurg, 66:161-171), who teach that in vitro assays cannot easily assess host-tumor and cell-cell interactions that may be important in the malignant state and

cannot duplicate the complex conditions of in vivo therapy. Thus in view of the above unpredictability, and further in view that cancer treatment is unpredictable, as overwhelmingly taught by the art, supra, one cannot extrapolate from in vitro lysis of a cancer cell line to a successful treating of patients having small cell lung cancer or neuroblastoma.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the unpredictability of cancer therapy, as indicated from the teaching of Kimmel et al, Gura, Jain, Curti, Hatrwell, Ezzell, Spitler, Boon and White, supra, and in view of the complex nature of the invention, a lack of sufficient disclosure in the specification, and little is known in the art concerning the claimed invention, it would have been undue experimentation for one of skill in the art to practice the claimed invention.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS

June 29, 2006